European Multicenter experience with Sutureless Perceval valve: clinical and hemodynamic outcomes up to 5 years in over 700 patients.

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This abstract will be presented at the 28th Annual Meeting of the European association of Cardio-thoracic Surgery in Milan from 11-15 October 2014.

Word count: Abstract: 245, Text: 2890

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Abstract

Objectives:

This report summarizes the 5-year clinical and haemodynamic data from three prospective, European multicenter trials with the Perceval suture-less aortic valve.

Methods:

From 4/2007 to 8/2012, 731 consecutive patients (mean age 78.5 years; 68.1% females; mean logistic EuroScore 10.9%) underwent AVR with the Perceval valve in 25 European centers. Isolated AVR was performed in 498 (68.1%) patients. Minimally invasive approach was performed in 189 (25.9%) cases. Cumulative follow- up was 729 patients-year.

Results:

In isolated AVR, mean cross-clamp and CPB times were 30.8 and 50.8 min in full sternotomy, and 37.6 and 64.4 min in minimally invasive approach, respectively.

Early Cardiac-related deaths occurred in 1.9%. Overall survival at 1 and 5 years were 92.1% and 74.7%, respectively.

Major paravalvular leak occurred in the 1.4% (early) and 1% (late follow up),

respectively. Significant improvement in clinical status was observed postoperatively in the majority of patients.

Mean and peak gradients decreased from 42.9 and 74.0 mmHg preoperatively, to 7.8 and 16 mmHg at 3-year follow-up. LV-mass decreased from 254.5 g to 177.4 g at 3 years.

Conclusions:

This European multi-center experience with largest cohort of patients with sutureless valves till date, shows excellent clinical and haemodynamic results that remain stable even up to 5 years follow-up. Even in this elderly patient cohort with 40% octogenarians, both early and late mortality were very low. There were no valve migrations, structural valve degeneration and valve thrombosis in follow-up.

The sutureless technique is a promising alternative to biological AVR.

Keywords: Aortic valve replacement, Sutureless heart valve prosthesis, Prospective study

Introduction

Aortic valve replacement (AVR) is the accepted ‘Gold Standard’ for the treatment of severe or symptomatic aortic valve stenosis. Due to increasing age of the patient population (reflecting the demographic changes) in the western world, the use of biological valves has increased over the past years. At the same time, a large proportion of these patients require concomitant surgical procedures in addition to AVR [1].

Although trans-apical or trans-femoral aortic valve implantations (TAVI) have been introduced for high risk patients, they are limited to patients with isolated aortic valve pathology [2].

Three consecutive European, multicenter, prospective, non-randomized clinical trials (Pilot, Pivotal, and CAVALIER) were designed to evaluate the sutureless Perceval aortic valve prosthesis in elderly patients. The Perceval valve (Sorin Group, Saluggia, Italy) is a bioprosthetic heart valve made of bovine pericardium allowing for a fast implantation through a sutureless technique. We describe the combined results of these three consecutive trials.

Material and Methods

Study design

This series comprises the cumulative results of patients undergoing aortic valve replacement with or without concomitant procedures from three consecutive European prospective multicenter trials (Pilot, Pivotal and CAVALIER), between 2007 and 2012.

25 centers in 8 European countries took part in these three studies. Approval for these studies was granted by the Ethical Committees of the Hospitals involved and each patient gave signed informed consent before being enrolled in the trials.

Perceval Pilot trial

The objective of the Pilot trial was to assess the safety of aortic valve replacement with the sutureless Perceval valve in 30 symptomatic patients, aged 75 and older. The primary endpoint was the assessment of the safety of the Perceval prosthesis in terms of mortality and morbidity at 30 days, correlated to prosthetic valve performance. Secondary endpoints were the evaluation of mortality and morbidity, the evaluation of the clinical status on the basis of the New York Heart Association (NYHA) functional classification, and the evaluation of the haemodynamic performance at 1, 3, 6 and 12 months from implantation, respectively.

Perceval Pivotal trial

The primary objective of the Pivotal study was to assess the performance of the Perceval valve at 3 to 6 months after implantation in 150 high surgical risk patients aged ≥75 years, requiring surgical intervention to replace the aortic valve. The primary endpoint was the assessment of the Perceval prosthesis safety and performance at 3 to 6 months after surgery. Secondary endpoints included the evaluation of the Perceval valve in terms of improvement of clinical status, haemodynamic performance by echocardiography, and assessment of mortality and morbidity rates at discharge and 12 months after implant, respectively.

These two Perceval trials aimed at obtaining initial CE mark approval, even though only two prosthesis sizes (Size S and Size M) were available. The outcomes showed adequate safety and performance, and allowed the Perceval to obtain CE mark in January 2011 (for sizes S and M) under limited indications.

CAVALIER trial

The CAVALIER trial was designed to assess the safety and effectiveness of the Perceval valve at 12 months after implantation when used to replace a diseased or dysfunctional aortic valve or aortic valve prosthesis in patients older than 65 years. The primary endpoint was the evaluation of the safety (assessed in terms of mortality and morbidity) and effectiveness (assessed in terms of improvement of clinical status as well as haemodynamic performance) of the

Perceval valve at 12 months after the implants. The secondary endpoints of the clinical investigation were the assessment of safety and effectiveness at discharge and 3 to 6 months after surgery and yearly thereafter. Besides lowering the age limit to younger patients (65 years or older), this study included two additional prosthesis sizes: Size L (from February 2010) and Size XL (from July 2012).

Perceval sutureless valve

The Perceval valve is a surgical bioprosthetic heart valve comprising a biological component of bovine pericardium and an elastic Ni-Ti alloy stent made of two rings and 9 vertical struts covered by a thin coating of Carbofilm™ that improves biocompatibility (Fig. 1). The stent has the dual task of supporting the valve and holding it in place without any permanent suture. Thanks to its elastic properties, the stent adapts to the anatomy of the aorta and follows its movements, relieving the stress on the leaflets. The valve is collapsed with an atraumatic device compression, assuring that the valve leaflets are not affected.

Surgical procedure

The patients were operated either through a standard median sternotomy or upper mini-sternotomy. Anaesthetic and surgical techniques were standardized according to the preferences of each centre. A transverse aortotomy was performed about 0.5 cm distal to the sinu-tubular junction in order to leave a free edge for closure of the aortotomy after implantation of the device.

The native calcified aortic valve was excised and the aortic annulus decalcified. A regular annular profile was beneficial to ensure optimal sealing and preventing the risk of paraprosthetic leak. The sizing of the annulus was done with the dedicated sizers.

For this series, the study valve was available in three sizes: Size S, to be implanted in annulus sizes from 19 to 21 mm, Size M to be implanted in annulus sizes from 21 to 23 mm, and Size L for patients with an annulus size from 23 to 25 mm.

The implantation technique included several steps as already described elsewhere [3, 4, 5].

Concomitant coronary artery bypass graft (CABG) procedures were additionally performed in patients with coronary artery disease. This was usually done during the time when the study valve was being collapsed to keep the aortic cross clamp time as short as possible.

After closure of the aortotomy in the usual fashion, release of the aortic cross clamp and thorough de-airing, the valve functioning was investigated by transesophageal echocardiography in all patients.

Following the procedure, the patients received anticoagulation treatment according to the standard protocol in use at each center for bioprostheses.

Patients:

From April 2007 to August 2012, a total of 765 patients were enrolled in these three Perceval studies (30 Pilot, 150 Pivotal and 585 Cavalier subjects). Out of

765 patients included in the study, the Perceval valve was implanted in 731 patients (95.6%), while in 34 cases (4.4%), conversion to commercially available valves was required.

The enrolment was carried out in a sequential, prospective manner such that all patients identified as candidates for standard aortic valve replacement with a bioprostheses (according to the practice of each centre) were offered the option of participating in the assessment if the they fulfilled the selection criteria defined in each protocol (Annex B).

Follow-up

According to the study protocol, clinical evaluation, ECG, blood exam and transthoracic echocardiographic examination were performed at discharge (or 30 days), at 3-6 months, at 12 months and then annually up to 5 years.

An Echo core laboratory performed a full analysis of the images and relevant calculations and an independent Clinical Events Committee reviewed and adjudicated the complications.

Adverse events were reported according to current guidelines [6]. Kaplan-Meier survival curve is shown in figure 2.

Statistical analysis

Statistical analyses were performed on all patients successfully implanted with a

Perceval valve. Categorical variables are reported as absolute and relative frequencies. For continuous data, means and standard deviations were calculated. Cumulative survival and freedom from events were estimated using the Kaplan-Meier method, with 95% confidence intervals (95% CI). Statistical analyses were performed using SAS software (Release 9.2, by SAS Institute Inc., Cary, NC, USA). A p-value <0.05 was considered to be statistically significant.

Results

Patient demographics and procedural outcomes

The mean age of the 731 patients was 78.5±5.3 years (range, 62-92 years). 43.1% of patients were ≥ 80 years old. The preoperative data are reported in

Table 1. The majority of patients presented with valve stenosis (509/69.6%) due to degenerative disease. Out of 731 patients, 542 patients (74.1%) underwent surgery via median sternotomy, whereas the remaining 189 patients (25.9%) underwent a minimally invasive surgical approach. Two hundred forty (32.8%) patients had concomitant procedures. In 192 (26.3%) patients, coronary artery bypass grafting was performed. Operative data are summarized in Table 2.

Mean aortic cross-clamp times and Cardio-pulmonary bypass (CPB) times were 30.8 min and 50.8 min respectively for isolated aortic valve replacement via median sternotomy and 37.6 min. and 64.4 min. for a minimally invasive approach (Table 3).

Complications

All-cause and cardiac early mortality were 3.4% (25/731) and 1.9% (14/731), respectively. Among the early cardiac deaths, 3 occurred in OR. One occurred during operation in a patient with very critical preoperative status; the patient underwent successful implant of the device that was then removed due to the presence of a previous endocarditic lesion and the patient did not survive the surgery due to myocardial failure. In second case, death was caused by an acute myocardial dysfunction, a third case was due to annulus rupture during traditional valve implantation following aortic regurgitation with the Perceval valve. All-cause and cardiac late mortality were 7% (51/731) and 1.4% (10/731), respectively.

Specific cause of early and late death is reported in Table 4.

During the follow-up phase, 21 patients required explantation of the Perceval valve, 10 early (1.4%), and 11 late.

Early explants

One case was related to a perioperative bleeding from the aorta: the patient was immediately returned to the operating room and had the Perceval valve as well as aortic root replaced with a biological valved conduit. The bleeding was caused by an aortic tear below the right coronary ostium, due to extensive decalcification of the annulus.

Two cases of early explants occurred at 2 and 4 days post-surgery and were likely due to mis-sizing leading to para or intra- prosthetic regurgitation; 3 cases occurred at 2, 3, and 7 days after surgery and were related to malpositioning and subsequent regurgitation; one Perceval was explanted at 12 days where a paravalvular leak (PVL) was caused by early endocarditis. One explant occurred at 13 days after surgery and was related to intra-valvular regurgitation in a patient with severe calcified aortic annulus requiring ascending aorta replacement. One explant occurred at 20 days after implant and was likely related to inappropriate sizing and positioning. A last case occurred at 30 days, secondary to deep valve positioning and consequent PVL.

Late Explants:

Among the 11 late explants (1.5%), 8 were due to endocarditis. An explant occurred at 122 days after surgery and was related to a shunt between aorta and right ventricle. This was initially diagnosed at discharge and considered not

haemodynamically significant, even though it later increased causing recurrent cardiac decompensation, pulmonary hypertension, and severe tricuspid regurgitation. One explant occurred around 19 months after surgery because of fibrous pannus overgrowth. One last late explant occurred at almost 2 years after implant and was due to a pseudo-aneurysm of the non-coronary sinus resulting in paravalvular regurgitation; the valve was replaced along with the ascending aorta.

Table 5 reports the early and late complications. Major paravalvular leak occurred in the 1.4% (early) and 1% (late follow up), respectively. The incidence of early major stroke was 1.6%, while 6 cases of late stoke events (0.8%) were reported. Forty-four patients (6.0%) with no prior history of cardiac rhythm disorders experienced early AV block III. Neither valve thrombosis nor structural valve deterioration was detected. No cases of valve migration or dislodgement after surgery were reported.

Clinical results:

The functional status significantly improved along with in the haemodynamic performance in the majority of the population. A marked decrease in NYHA stage was observed with the majority of patients falling in class I-II during follow-up. The mean gradient was 10.3 mmHg at discharge/1 month, 8.9 mmHg at 3-6 months and 12 months, 8.8 mmHg at 2 years, and 7.7 mmHg and 7.8 mmHg at 3 and 4 years, respectively. At 5 year follow up, the few data available at the time of the data analysis (6 echo exams) showed a mean gradient of 7.8 mmHg. This gradient reduction was correlated to an increase in the effective

orifice area from 0.75 cm^2 preoperatively to 1.49 cm^2 at discharge/1 month, 1.51 cm^2 at 3-6 months, 1.55 cm^2 at 12 months, up to 1.80 cm^2 at 5 years, and to a LV-mass regression, which went from 254.5 g to 177.4 g at 3 years. Hemodynamic results by valve size are reported in Table 6.

Discussion

Aortic valve replacement has been widely accepted as the gold standard for the treatment of patients with aortic valve stenosis [7]. The mean age of the patients referred for AVR has been increasing along with the demographic changes. In the present study cohort more than 40% of the patients were 80 years or older. The 5-year outcomes from patients undergoing AVR with Perceval valve demonstrate that the device is safe and well performing, even in a old population with co morbidities.

Previous studies demonstrated that the duration of aortic cross-clamping and CPB are independent predictors of survival after either aortic valve replacement or combined valve operations with CABG [8, 9]. Therefore, a new technology for shortening aortic cross-clamp time and consequently CPB time is mandatory to further reduce mortality after AVR surgery.

The Perceval valve features a fairly high adaptability to different surgical approaches as showed by this study. The implantations were performed either via full sternotomy or minimally invasive approach (mini-sternotomy or right anterior mini-thoracotomy) [10, 11].

Previous experiences showed that the use of less invasive AVR was associated

with excellent outcomes in terms of postoperative complications and hospital stay [12, 13]. However the reduced working space for the exposure and implantation of the prosthetic valves (especially in small or calcified aortic annuli) presented the drawback of the increasing surgical times. In such cases the adoption of sutureless technology may facilitate the less invasive AVR approach. In this study the low cross-clamp times, that were achieved with both surgical approaches, demonstrates the ease of implantation of the Perceval valve.

The possibility of performing simultaneous procedures, in particular CABG, with this device represents an advantage as compared to other interventional techniques, such as trans-catheter aortic valve implantations (TAVI). This is important as according to the STS database, the proportion of candidates requiring concomitant CABG has risen from 5% to 25% over the past 20 years. Previous experience already demonstrated the safety and efficacy of the Perceval valve even in cases of concomitant cardiac procedures. [14].

In patients requiring aortic valve replacement along with concomitant procedures, shortening the aortic cross clamp and CPB time may help reduce the mortality and morbidity. Ranucci et al. [9] reported that the aortic cross clamp time is an independent predictor of severe cardiovascular morbidity, with an increased risk of 1.4% per one minute increase. Therefore, the use of sutureless valves may help reduce the procedural times thanks to the absence of need for sutures.

The clinical results up to 5 years follow-up reported in this large cohort of patients, confirm the safety and efficacy of the Perceval sutureless aortic valve. Rates of early and late mortality and complications such as stroke, PVL are comparable with reported rates for traditional AVR [15,16]. Even in cases requiring explantation of the Perceval, the procedure was easy and the Perceval valve was removed without technical issues, as previously described [17].

New occurrences of early AV block III leading to pacemaker implant in patients with no prior history of cardiac rhythm disorders was 6.0%, which is within the ranges reported in literature for traditional AVR [18]. This rate could also be related to the initial learning curve effect. Additionally, the large number of centers in this cohort and variability of operators and protocols of rhythm disorders management could be considered as an additional potential contributing factor, considering that in one of the biggest cohort in experienced centers, the rate was lower (4.2%) [19].

No valve dislodgement or migration, thrombosis or structural valve deterioration was observed even after a follow-up of up to 5 years.

The valve implantation resulted in significant improvement of patient's symptoms. Even though a majority of patients were quite short in stature with small aortic annulus and received small size prostheses, the post-operative trans-valvular gradients were low and remained stable over time up to 5 years follow-up. In patients with a critically small annulus, this valve allows maximization of the bioprosthetic diameter, as previously reported [20]. The haemodynamic data show an improvement of the left ventricular function.

Conclusions

In summary, this study reports the widest and longest experience with a sutureless valve and highlights its safety and efficacy also in an elderly population. The Perceval implant could be easily performed by offering a significant reduction of cross clamping and cardiopulmonary bypass times with respect to both the traditional valve prostheses and the other sutureless prostheses available on the market [21, 22, 23], even when performed via minimally invasive approach. Therefore, in patients needing aortic valve replacement with or without concomitant procedures, this device could have an advantage compared to conventional sutured valves. The continuation of the patient follow-up will provide further assessment of long-term valve performance.

Limitation

One limitation of this study is that there is no control group with patients receiving conventional valves to determine the Perceval additional benefits respect to the gold standard. Furthermore, EuroScore was used for the three studies even though EuroScore may overestimate risk of mortality.

Disclosure:

The participating centers received an unrestricted study grant from Sorin to conduct this study. The following authors are consultants/proctors for Sorin: M. Shrestha, T. Fischlein, B. Meuris, M Misfeld and F. Laborde.

References

1. Beckmann A, Funkat AK, Lewandowski J et al. Cardiac Surgery in Germany during 2012: A Report on Behalf of the German Society for Thoracic and Cardiovascular Surgery. Thorac Cardiovasc Surg 2014;62:5-17.
2. Cribier A, Eltchaninoff H, Bash A et al. Percutaneous transcatheter

implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. Circulation 2002;106:3006-8.

3. Shrestha M, Folliguet T, Meuris B et al. Sutureless Perceval S aortic valve replacement: a multicenter prospective pilot trial. J Heart Valve Dis 2009;18:698-702.
4. Folliguet TA, Laborde F, Zannis K, Ghorayeb G, Haverich A, Shrestha M. Sutureless perceval aortic valve replacement: results of two European centers. Ann Thorac Surg 2012;93:1483-8.
5. Flameng W, Herregods MC, Hermans H et al. Effect of sutureless implantation of the Perceval S aortic valve bioprosthesis on intraoperative and early postoperative outcomes. J Thorac Cardiovasc Surg 2011;142:1453-7.
6. Akins CW, Miller DC, Turina MI et al; STS; AATS; EACTS. Guidelines for reporting mortality and morbidity after cardiac valve interventions. J Thorac Cardiovasc Surg 2008;135:732-8.
7. Schwarz F, Baumann P, Manthey J et al. The effect of aortic valve replacement on survival. Circulation 1982;66:1105-10.
8. Flameng WJ, Herijgers P, Szecsi J, Sergeant PT, Daenen WJ, Scheys I. Determinants of early and late results of combined valve operations and coronary artery bypass grafting. Ann Thorac Surg. 1996;61:621-8.
9. Ranucci M, Frigiola A, Menicanti L, Castelvecchio A, De Vincentiis C, Pistuddi V, for the Surgical and Clinical Outcome Research (SCORE) Group. Aortic Cross-Clamp Time, New Prostheses, and Outcome in Aortic Valve Replacement. The Journal of Heart Valve Disease 2012;21:732-739

10. Santarpino G, Pfeiffer S, Schmidt J, Concistre G, Fischlein T. Sutureless aortic valve replacement: first-year single-center experience. Ann Thorac Surg 2012;94:504–9.
11. Gilmanov D, Farneti P, Miceli A, Bevilacqua S, Glauber M. Perceval S sutureless aortic valve prosthesis implantation via right anterior minithoracotomy. Multimed Man Cardiothorac Surg 2013.
12. Murtuza B, Pepper JR, Stanbridge RD, Jones C, Rao C, Darzi A, et al. Minimally access aortic valve replacement: is it worth it? Ann Thorac Surg. 2008;85:1121-31.
13. Brown ML, McKellar SH, Sundt TM, Schaff HV. Ministernotomy versus conventional sternotomy for aortic valve replacement: a systematic review and meta-analysis. J Thorac Cardiovasc Surg. 2009;137:670-9.
14. Aortic Valve Replacement and Concomitant Procedures With the Perceval Valve: Results of European Trials. Shrestha M, Folliguet TA, Pfeiffer S, Meuris B, Carrel T, Bechtel M, Flameng WJ, Fischlein T, Laborde F, Haverich A. Ann Thorac Surg. 2014 Aug 5. pii: S0003-4975(14)01085-6.
15. Hamm CW, Möllman H, Holzhey D et al. The German Aortic Valve Registry (GARY): in-hospital outcome. European Heart Journal doi:10.1093/eurheartj/eht381.
16. Ionescu A, Fraser AG, Butchart EG. Prevalence and clinical significance of incidental paraprosthetic valvular regurgitation. Heart. 2003;83:1316-21.
17. Santarpino G, Pfeiffer S, Concistrè G, Fischlein T. A supra-annular malposition of the Perceval S sutureless aortic valve: the ‘χ-movement’ removal technique and subsequent reimplantation. Interactive

CardioVascular and Thoracic Surgery 15 (2012) 280–281.

18. Matthews IG, Fazal IA, Bates MGD, Turley A. In patients undergoing aortic valve replacement, what factors predict the requirement for permanent pacemaker implantation? Interactive CardioVascular and Thoracic Surgery 12 (2011) 475–479.
19. Miceli A, Santarpino G., Pfeiffer S., Murzi M., Gilmanov D., Concistre G., Quaini E., Solinas M, Fischlein T., Glauber M. Minimally invasive aortic valve replacement with Perceval S sutureless valve: Early outcomes and one-year survival from two European centers. J Thorac Cardiovasc Surg 2014;-:In Press
20. Shrestha M, Maeding I, Höffler K et al. Aortic valve replacement in geriatric patients with small aortic roots: are sutureless valves the future? Interact Cardiovasc Thorac Surg 2013;17:778-82.
21. www.sts.org/documents/pdf/Spring2005STS ExecutiveSummary.pdf
22. Kocher AA, Laufer G, Haverich A, Shrestha M, Walther T, Misfeld M, Kempfert J, Gillam L, Schmitz C, Wahlers TC, Wippermann J, Mohr FW, Roth M, Skwara A, Rahmanian P, Wiedemann D, Borger MA. One-year outcomes of the Surgical Treatment of Aortic Stenosis With a Next Generation Surgical Aortic Valve (TRITON) trial: a prospective multicenter study of rapid-deployment aortic valve replacement with the EDWARDS INTUITY Valve System. J Thorac Cardiovasc Surg. 2013 Jan;145(1):110-5; discussion 115-6.
23. Martens S, Sadowski J, Eckstein FS et al. Clinical experience with the ATS 3f Enable® Sutureless Bioprosthesis. Eur J Cardiothorac Surg 2011;40:749-

55.

Annex A: Physicianss and surgical sites involved in the study

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Annex BStudies inclusion and exclusion criteria

Inclusion Criteria	**Exclusion Criteria**
1. ≥ 75 years (Pilot and Pivotal Trials), ≥ 65 years (CAVALIER Trial);	1. Subjects involved in any other clinical study for drugs or devices
2. Subjects with aortic valve stenosis or steno-insufficiency;	2. Subjects with a previously implanted Perceval prosthesis, within the clinical study, that requires replacement
3. Subjects in which preoperative evaluation indicated the need for native or prosthetic aortic valve replacement with a biological prosthesis;	3. Subjects with previous implantation of valve prostheses or annuloplasty ring not being replaced by the study valve
4. Subjects willing to sign the informed consent;	4. Subjects requiring simultaneous cardiac procedures, apart from septal myectomy and/or coronary by-pass
5. Subjects willing to undergo all the medical follow-ups and echocardiography examinations and laboratory tests that form part of this present protocol.	5. Subjects who require double or multiple valve replacement or repair in whom the mitral, tricuspid, or pulmonic valve would be replaced with a non-Perceval valve or repaired

	6. Subjects with aneurysmal dilation or dissection of the ascending aortic wall
	7. Subjects needing non elective intervention
	8. Subjects with active endocarditis
	9. Subjects with active myocarditis
	10. Subjects with congenital bicuspid aortic valve
	11. Subjects with aortic root enlargement, where the ratio between the diameter of the sino-tubular junction and the annulus diameter, assessed by TTE, is > 1.3
	12. Subjects with aortic root height (measured from aortic annulus to sino-tubular junction) ≥ 21 mm for size S/21, ≥ 22.5 mm for size M/23, ≥ 24 mm for size L/25
	13. Subjects with myocardial infarction ≤ 90 days before the planned valve implant surgery
	14. Subjects with known

	hypersensitivity to nickel alloys
	15. Subjects involved in any other clinical study for drugs or devices
	16. The subject is a prison inmate, institutionalized, or is unable to give informed consent;
	17. The subject has a major or progressive non-cardiac disease that, in the investigator's experience, results in a life expectancy of less than 1 year, or the implant of the device produces an unacceptable increased risk to the patient;
	18. The subject is undergoing renal dialysis for chronic renal failure or has hyperparathyroidism;
	19. The subject has an acute preoperative neurological deficit, myocardial infarction, or cardiac event that has not returned to baseline or stabilized ≥ 30 days prior to the planned valve implant surgery.

Table 1: Preoperative characteristics and risk factors (mean ± std).

Patients	**N=731**	**%**
Sex		
F	498	68.1
M	233	31.9
Mean age ± SD (range)	78.5±5.3 (62.0-92.0)	
Patients ≥ 80 years	315	43.1
Mean Height ± SD (range) (cm)	162.9±7.9 (140.0-186.0)	
Mean Weight ± SD (range) (Kg)	72.4±13.4 (38.0-112.0)	
Mean BSA ± SD (range)	1.8 ± 0.2 (1.3 - 2.4)	
Risk Factors[a]		
Systemic hypertension	589	80.6
Diabetes	203	27.8
Smokers	155	21.2
Extracardiac arteriopathy	117	16.0
Renal insufficiency	108	14.8
Cerebrovascular disease	75	10.3
Previous Cardiovascular Surgery[b]		

CABG	14	1.9
Previous valve surgery	7	1.0
CABG + previous valve surgery	1	0.4
NYHA		
I	19	2.6
II	163	22.3
III	488	66.8
IV	42	5.7
Not available	19	2.6
Type of valve lesion		
Stenosis	509	69.6
Steno-Insufficiency	221	30.2
Insufficiency	1	0.1
Mean EuroScore ± SD (range)	10.9 ± 8.2 (1.2 - 75.3)	
Mean STS Score ± SD (range)	8.5 ± 8.6 (0.8 - 67.5)	
Rhythm disorders		
Previous atrial fibrillation/flutter	88	12.0
Previous heart block	52	7.1

a: Risk factors patient could have more than 1 risk factor; b: Patient can have more than one previous surgery

Table 2: Operative data.

Patients	**N=731**	**%**
Surgical approach		
Median sternotomy	542	74.1
Minimally invasive approach	189	25.9
Aortic valve condition		
Tricuspid	714	97.7
Bicuspid	8	1.1
Other (7 previous bioprostheses, 1 pseudo bicuspid, 1 monocusp)	9	1.2
Valve Size		
S/21	122	16.7
M/23	383	52.4
L/25	226	30.9
Concomitant Procedures [a]		
None	491	67.2
Concomitant procedures	240	32.8
CABGs	192	26.3
Septal myectomy	27	3.7
Other cardiac concomitant procedures	27	3.7
Other non cardiac concomitant procedures	11	1.5

[a] patients can have more than one procedure

Table 3: Procedure timings.

	Isolated AVR (N=498)	**Concomitant cardiac procedure (N=233)**	**OVERALL (N=731)**
	Mean (SD)	Mean (SD)	Mean (SD)
Median sternotomy			
CPB time	50.8 (19.5)	79.5 (33.3)	62.4 (29.5)
X-clamp time	30.8 (10.8)	51.5 (23.6)	39.2 (19.9)
Minimally invasive			
CPB time	64.4 (19.2)	68.5 (23.1)	64.7 (19.5)
X-clamp time	37.6 (12.0)	42.6 (13.7)	37.9 (12.1)
Overall			
CPB time	55.8 (20.5)	78.9 (32.9)	63.0 (27.2)
X-clamp time	33.3 (11.7)	51.0 (23.2)	38.8 (18.2)

Table 4: Specific causes of early (≤30 days) and late (> 30 days) deaths

	Early N = 25	**Late N = 51**
Cardiac	**N= 14 (days post-op)**	**N = 10 (days post-op)**
In OR	3	
Heart failure	2 (1, 4)	6 (40, 85, 105, 302, 395, 902)
Rhythm troubles	5 (0, 4, 6, 16, 23)	
Endocarditis	1 (13)	1 (264)
Multiorgan failure	1 (11)	1 (191)
Cardiac insufficiency	2 (19, 24)	
Sepsis		1 (685)
Stroke		1 (58)
Non cardiac	**N= 8 (days post-op)**	**N= 30**
Multiorgan failure	4 (7, 14, 29, 29)	4 (40, 45, 55, 101)
Liver insufficiency	1 (4)	
Gastro-intestinal bleeding	1 (18)	
Neurological vascular accident	1 (30)	
Sepsis leading to respiratory insufficiency and coma	1 (30)	
Sepsis		2 (33, 43)

Infections		7 (33, 41, 55, 67, 154, 682, 733)
Renal failure		5 (181, 311, 329, 361, 432)
Diarrhea and dehydratation		1 (60)
Respiratory insufficicency		2 (37, 40)
Neoplastic pathology		4 (49, 84, 220, 297)
Autoimmune thrombocytopenia		1 (71)
Accident		1 (76)
Cerebral bleeding		1 (670)
Cerebral hematoma due to fall		1 (204)
Worsening of COPD		1 (170)
Sudden, unexpected, unexplained	N= 3 (13, 24, 28)	N= 11 (34, 76, 82, 88, 152, 165, 376, 443, 602, 1196, 1267)

Table 5: Haemodynamic performance as evaluated by transthoracic echocardiography (Mean ± SD).

	Preoperative	Discharge/1 month	3-6 months	12 months	2 years	3 years	4 years	5 years
LVEF [%]	60.1±11.6	58.4±11.2	60.7±9.9	61.4±9.9	67.0±8.5	67.0±9.0	66.1±9.1	65.8±7.7
size 21	63.8±12.9	62.1±10.0	62.7±9.9	64.9±8.9	65.5±11.1	68.1±5.8	64.3±5.1	64.0±4.2
size 23	61.9±11.1	60.6±10.7	62.7±9.6	63.2±8.6	67.9±7.5	66.4±10.8	67.0±10.9	67.0±10.1
size 25	55.1±10.0	52.9±10.4	55.9±8.6	55.5±10.5	56.0	NA	NA	NA
MPG [mmHg]	42.9±16.4	10.3±4.4	8.9±4.3	8.9±4.7	8.8±3.9	7.7±2.8	7.8±3.8	8.8±4.6
size 21	43.4±17.7	10.9±5.1	10.5±6.3	10.2±5.2	8.2±3.4	9.7±3.0	8.7±4.0	10.5±7.8

size 23	41.8±15.9	10.5±4.5	8.9±4.0	8.8±4.9	9.0±4.1	6.8±2.3	7.5±4.0	8.0±3.6
size 25	44.7±16.6	9.5±3.8	8.0±3.2	8.2±3.7	7.8	NA	NA	NA
PPG [mmHg]	74.0±25.6	20.4±8.5	17.8±7.7	17.7±8.0	20.0±7.9	16.0±5.2	17.8±8.1	21.1±9.7
size 21	78.8±27.9	22.6±10.6	21.0±9.0	20.7±9.7	19.4±5.7	19.0±4.5	20.6±9.3	27.0±15.5
size 23	72.5±24.6	21.1±8.4	18.3±7.8	17.6±7.8	20.3±8.5	14.6±5.0	16.7±8.0	18.2±6.4
size 25	73.6±25.7	17.9±6.5	15.1±5.5	15.8±6.3	14.3	NA	NA	NA
EOA [cm^2]	0.75±0.23	1.49±0.39	1.51±0.37	1.55±0.37	1.70±0.46	1.64±0.42	1.68±0.43	1.80±0.30
size 21	0.75±0.27	1.40±0.37	1.40±0.37	1.47±0.37	1.71±0.49	1.44±0.22	1.40±0.30	1.55±0.09
size 23	0.76±0.23	1.52±0.41	1.51±0.38	1.56±0.40	1.71±0.46	1.74±0.46	1.79±0.44	1.92±0.30

size 25	0.73±0.19	1.49±0.35	1.56±0.37	1.57±0.31	1.19	NA	NA	NA
LVMASS [g]	254.5±77.6	238.6±74.3	216.2±66.5	216.6±70.6	188.6±66.1	177.4±46.9	116.0±12.7	227.7±74.3
size 21	224.0±64.4	190.0±63.0	169.9±49.5	180.7±59.6	142.0±80.6	174.2±57.3	107.0	266.5±44.5
size 23	253.7±79.2	233.8±70.8	214.3±65.7	212.8±68.5	185.4±54.3	179.1±43.9	125.0	150.0
size 25	269.5±77.1	262.6±73.7	241.8±62.8	242.5±70.6	316.0	NA	NA	NA

Table 6: Observed postoperative adverse events rates. All patients, n=731.

Cumulative follow-up = 729 pts-yr

	Total		Early events (≤30 days)		Late events (>30 days)		
	n	%	n	%	n	%	%/pts-yr

Deaths	76	10.4	25	3.4	51	7.0	7.0	(5.4-8.6)
Cardiac	24	2.1	14	1.9	10	1.4	1.4	(1.2-1.6)
Non-cardiac	38	5.2	8	1.1	30	4.1	4.1	(2.9-5.3)
Sudden, Unexpected, Unexplained Death/Unknown	14	1.9	3	0.4	11	1.5	1.5	(0.8-2.2)
Explants	21	2.9	10	1.4	11	1.5	1.5	(0.8-2.2)
Stroke	18	2.5	12	1.6	6	0.8	0.8	(0.3-1.3)
Intra-prosthetic regurgitation	5	0.7	4	0.6	1	0.1	0.1	(0.0-0.3)
Minor	2	0.3	2	0.3	0	0.0	0.0	-
Major	3	0.4	2	0.3	1	0.1	0.1	(0.0-0.3)
Paravalvular leak	19	2.6	10	1.4	9	1.2	1.2	(0.6-1.9)
Minor	2	0.3	0	0.0	2	0.3	0.3	(0.0-0.6)
Major	17	2.3	10	1.4	7	1.0	1.0	(0.4-1.6)
Endocarditis	14	1.9	2	0.3	12	1.6	1.7	(0.9-2.4)
AV block III	79	10.8	65	8.9	14	1.9	1.9	(1.1-2.8)

AV block III in patients without preoperative cardiac rhythm abnormalities	54	7.4	44	6.0	10	1.4	1.4	(1.2-1.6)

Figure Legend: